Irvin M Modlin M.D., Ph.D., F.A.C.S., F.R.C.S.
Professor, Department of Surgery
Director, Gastric Surgical Pathobiology Research Group
Director, G.I. Endoscopic Surgery
Department of Surgery
Yale University School of Medicine
P.O. Box 208062
New Haven, CT 06520-8062

Dr. Modlin's current position is Professor of Surgery, Yale University School of Medicine. Dr. Modlin was educated at the University of Cape Town, Royal PostGraduate Medical School Hammersmith Hospital London, and UCLA. His scientific interests molecular physiology with a specific interest in neuroendocrine cell tumor biology. Current areas of research include the characterization of the somatostatin receptor, regulation of cell transformation and neurotransmitter modulation of cell proliferation. Clinical interests include a special focus on gastro intestinal endocrine surgery, the development of isotopic therapy for the treatment of neuroendocrine tumors and regulation of parietal cell proton pump function by gastric enterochromaffin like cells. Dr. Modlin has authored over 300 articles and a dozen books including cell physiology, clinical material, laparoscopy, medical history, travel and biography.

The Rationale of Indium Labeled Octreotide Therapy

Irvin M Modlin, John Murren, G Cornelius, S Zogby.
Yale University, School of Medicine

The therapy of malignant lesions of the gastrointestinal tract has made significant progress over the course of the century. This reflects a number of major advances that have occurred both in biology and clinical medicine. The initial recognition that cancer was a specific type of lesion and not an inflammation or infection led to a paradigm shift in the concepts engendered in its management. The advent of anesthesia and antisepsis emboldened individuals possessed of dexterity and the courage of their convictions to surgically seek cure by ablation of the lesion and large areas of contiguous or adjacent structures. Despite initial enormous enthusiasm and considerable verve almost 100 years utilizing this strategy have demonstrated that this approach is only of use in early lesions. Metastatic spread particularly of the microscopic variety is rarely adequately dealt with by major surgery. Alternative modalities that have been utilized have sought to either destroy proliferating cells =(cytotoxic therapy) or sterilize entire areas by exposure to field radiation of various kinds. Both of these techniques have only limited success since they are non-selective and in addition also damage normal tissue and cells.

It is thus apparent that despite the passage of time and the further delineation of tumor cell biology the critical issue in managing tumor already in place is the development of site or cell specific therapy. In this respect the critical requirement is the location of a unique target on a specific cell or the ability to selectively target only one kind of cell. A further issue is the need to identify an agent capable of generating cell death or proliferative arrest which is non toxic to other systems of the body and yet lethal to the cell in question. Neuroendocrine tumors express large numbers of somatostatin receptors and neoplastic cells of neuroendocrine origin usually retain this property. The development of an analogue of somatostatin (octreotide) capable of selectively binding to the SSTR2 of such tumor cells provided a unique therapeutic opportunity to control secretion and proliferation of such lesions since SST exerts a profound inhibitory effect. Nevertheless such therapy has not proven particularly effective since other regulatory agents (genomic events or growth factors) are still operative and tumor growth is only stabilized and rarely abrogated. Since relatively modest doses of indium bound to octreotide are specific in identifying such NETs it was proposed that the utilization of larger quantities of the isotope might

be useful in delivering site specific isotopic therapy to cells expressing SSTR2. Experimentally we have demonstrated significant receptor uptake and internalization of indium labeled octrotide with resultant exposure of nuclear proteins to Auger electron radiation. This is particularly limited in its distribution and thus its effects are limited to local tumor cells. We have successfully conjugated up to 300 mCi indium to octreotide and delivered it intravenously to patients with a variety of NETs. A total of 17 patients have been treated with no adverse effects over a period of 2 years. Stabilization of tumor growth has occurred in 8 patients, 2 of whom had marked clinical improvement in their functional status, and regression in 2. The lack of renal, gut, bone marrow disturbance has been striking. In addition patients experience no alteration in health related well being from the treatment and are back at work within 24hrs.Given the evolution of cancer therapy over the last century it seems likely that one of the avenues that requires extensive exploration at this time is the cell specific delivery of radiotherapy to tumor cells. Its application will increase cell kill, improve survival and avoid the local damage and systemic toxicity engendered by therapeutic strategies currently available. Since the cost of such therapy is no greater than cytotoxic therapy and external beam radiation and far more cost effective in terms of quality of life and productivity terms its development has considerable merit. Current human clinical data are sufficiently encouraging to warrant the identification of other cell specific receptor targets and more effective isotopes as part of the development of a valid novel therapeutic strategy.